Remarks

The foregoing amendments are believed to place the claims in condition for allowance or in better condition for consideration on appeal. 37 C.F.R. § 1.116(a). Accordingly, their entry after final rejection is respectfully requested.

I. Status of the Claims

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 146-244 are pending in the application, with claims 146-148, 176-177, 204-206, and 233 being the independent claims. Claims 146-148, 176-177, and 204-206 have been amended to recite that the Actinidia extract is *orally administered.* The dependency of claim 228 has been amended so that it now depends from claims 204-206. Claims 166, 195, and 224 have been amended to further characterize the kiwifruit extracts produced by the methods of claims 165, 194, and 223. Claims 176 and 177 have been amended so that "systemic lupus erythematosus" replaces "system lupus erythematosus." New claims 233-244 are sought to be added. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

II. The Amendments

Claims 146-148, 176-177, and 204-206 have been amended to recite that the Actinidia extract is *orally administered.* Support for this amendment can be found in the specification, *inter alia*, at page 4, lines 3-12, page 5, lines 13-21, page 6, lines 18-25 page 8, lines 24-32 and page 9, line 8 through page 10, line 15.

New claims 233-244 are directed to treating, alleviating or reducing one or more symptoms of allergy in a mammal suffering from food allergy, atopic dermatitis or allergic rhinitis via the oral administration of an extract of kiwifruit from the genus Actinidia. Support for these claims can be found in the specification, *inter alia*, at page 4, lines 3-12, page 5, lines 13-31, page 6, lines 5-7 and lines 31-32, page 7, lines 6-10 and lines 20-32, and page 9, lines 1-3.

Accordingly, no new matter is believed to have been added by the amendments, and their entry is respectfully requested.

III. Statement of Substance of Interview

Applicants thank the Examiner for the courtesy of the in-person interview held on March 31, 2009, with Applicants' representative, Timothy J. Shea, Jr., regarding the present application and Office Action. During that interview, Applicants' representative and Examiner discussed the Office Action, pending claims, and original disclosure. The Examiner indicated that Applicants' reply will be reviewed for determination of allowability. Further to the interview, Applicants provide herein arguments for further consideration.

IV. The Rejections

A. Rejection Under 35 U.S.C. § 112, first paragraph

Claims 146, 149-176, 204, and 208-232 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. (*See* Office Action, page 3). Applicants respectfully traverse this rejection.

1. Legal Principles of the Enablement Requirement

The test for enablement is whether one of ordinary skill in the art, given the disclosure at the time of filing, could make and use the claimed invention without undue experimentation. *See In re Wands,* 858 F.2d 731, 737 (Fed. Cir. 1988). In order to establish a *prima facie* case of lack of enablement, *the Examiner has the initial burden* to set forth a reasonable basis to question the enablement provided for the claimed invention. *See In re Wright,* 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). To satisfy this burden, "it is incumbent upon the Patent Office... to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to *back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.*" *See In re Marzocchi,* 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971) (emphasis added).

2. The Examiner Has Not Met the Burden of Showing a Lack of Enablement

The Examiner asserts in the Office Action that Applicants' specification "does not enable any person skilled in the art . . . to practice the invention commensurate in scope with these claims." Yet the Examiner has failed to provide any sound reasoning or objective technical evidence whatsoever to support this broad assertion. *Indeed,*

conspicuously absent from the rejection, which spans pages 2-6 of the Office Action, is a single cite to the scientific literature that would refute or even cast doubt upon the teachings or data in Applicants' specification.

In fact, the claimed methods have been exemplified in numerous Experimental Examples such that a person of ordinary skill in the art at the time of filing would have been able to practice the invention commensurate in scope with the claims without undue experimentation. Since no specific scientific evidence or reasoning has been presented to indicate otherwise, the reasons for the rejection are insufficient to establish a *prima facie* case of non-enablement.

Applicants below address each of the *Wands* factors cited by the Examiner in the Office Action. When the specification is analyzed in light of these factors, it is clear that the claimed invention is fully enabled.

a. The nature of the invention

Regarding the nature of the invention, the Examiner generally describes the rejected claims as being drawn to methods for inhibiting or reducing IgE production or inhibiting histamine release in a mammal in need thereof via the administration of an extract of kiwifruit of the genus Actinidia in order to treat, alleviate, or reduce symptoms of specific allergic diseases recited in claim 146. (Office Action at page 4).

Applicants submit that this broad characterization of the rejected claims fails to recognize the important distinctions between independent claims 146, 176, and 204. For example, claim 146 differs in scope with claim 204 as the former claim is directed to a method of treating *specific allergic diseases* by reducing or inhibiting IgE production with extracts from *any kiwifruit* of the genus Actinidia, whereas the latter claim is

directed to a method of treating *all allergic diseases* with extracts from *Actinidia arguta, Actinidia polygama or Actinidia kolomikta*. Claims 146 and 204 additionally differ from claim 176 in that claim 176 is directed to a method of treating *specific allergic or non-allergic inflammatory diseases* by inhibiting *histamine release* with extracts from *any kiwifruit* of the genus Actinidia in a mammal in need thereof.

Therefore, the nature of invention as it relates to the rejected claims encompasses inhibiting or reducing IgE production or inhibiting histamine release via the oral administration of specified kiwifruit extracts to treat, alleviate or reduce one or more symptoms of specified allergic or non-allergic inflammatory diseases.

b. The state of the prior art

In addressing the second *Wands* factor, the state of the prior art, the Examiner fails to make any attempt to characterize the prior art at the time of Applicants' invention. Not a single journal article is cited as evidence of the state of the art. Rather, the Examiner makes the conclusory assertion that the specification fails to provide guidance "as to a specific protocol to be utilized in order to show the efficacy of the presently claimed inhibition or reduction of IgE production and histamine release in a mammal." It is not clear to Applicants how this relates to the state of the prior art. Moreover, the assertion is incorrect, and Applicants submit that the Examiner has not met the initial burden of showing a lack of enablement.

As of the filing date of the present application, numerous *in vitro* and *in vivo* models suitable for studying allergic and non-allergic inflammatory conditions were known to those of skill in the art. In addition, the specification provides ample guidance

by teaching how to inhibit or reduce IgE production or inhibit histamine release in a mammal in need thereof.

(1) In vitro/In vivo Allergic Response Models

At the time of filing, both *in vitro* and *in vivo* models useful for studying allergic responses were well known to those of skill in the art. The specification provides examples of established models for both *in vitro* and *in vivo* allergic response analysis, that are described in further detail below. (*See* U266B1 human myeloma cell line at Example 3 for *in vitro* allergic response analysis and ovalbumin-sensitized and Nc/Nga mice at Examples 2 and 7, respectively for *in vivo* allergic response analysis in the specification.)

The U266B1 human myeloma cell line has long been known as a useful tool for studying the molecular basis of the allergic response *in vitro*. *See* Hall, T.J. and Brostoff, J. *Immunol. 77*:462-464 (1992) and Kimata, H. and Saxon, A. *Int. Arch. Allergy Appl. Immunol. 82*:419-421 (1987) (Exhibits A and B, respectively). Due to the fact that U266B1 cells produce IgE at elevated levels as compared to other non-induced human B cell lines, numerous researchers have used this cell line over the years in an attempt to identify potentially-therapeutic molecules for the treatment of IgE-mediated allergic diseases.

The specification also provides an established *in vitro* allergy model useful for evaluating histamine release. Experimental Example 5 of the specification describes inhibition of histamine release from mice peritoneal mast cells that were treated with kiwifruit extracts prior to stimulation with the DNP_{24}-BSA antigen. This *in vitro* model

had been used by researchers since at least 1968 to show that antigen-induced histamine release from peritoneal mast cells is correlated with the production of anaphylactic antibodies in mice. *See* Prouvost-Danon, A. *et al., Immunol. 15*:271-286 (1968) (Exhibit C).

In addition, Herz U. *et al.*, provides an excellent review of an *in vivo* allergic mouse model. *See* Herz U. *et al., Methods 32*:271-280 (2004) (Exhibit D). Herz *et al.* discuss at length how particular IgE-high responding strains of ovalbumin-sensitized BALB/c mice were identified for *in vivo* modeling of human allergic responses. Typical molecular responses observed in these mice when exposed to ovalbumin are elevated levels of IgE, IL-4 and IL-5 and the recruitment of eosinophils into inflamed tissue.

Another *in vivo* model for allergic response study is the NC/Nga mouse model. As discussed in Matsuda *et al.* (Exhibit E), the NC/Nga mouse model had been utilized as early as 1955 and is known for its "high susceptibility to anaphylactic shock from ovalbumin." *See* Matsuda H. *et al. Int. Immunol. 9*:461-466 (1997). Matsuda *et al.* further discloses that NC/Nga mice "spontaneously [suffer] from dermatitis, with clinical and histological features similar to human [atopic dermatitis]." Vestergaard, C. *et al.* (Exhibit F), discusses the overproduction of T_H2-specific cytokines in NC/Nga mice exhibiting atopic dermatitis-like lesions. *See* Vestergaard, C. *et al., J. Clin. Invest. 104*:1097-1105 (1999). *Indeed the NC/Nga mouse has been found to be "a suitable model for certain aspects of human [atopic dermatitis]" with clinical features including hyperproduction of IgE and elevated levels of IL-4 and IL-5. See* Matsuda *et al.* at page 464.

Thus, Applicants respectfully submit that the state of the art was such that one of ordinary skill in the art at the time of filing would know that assays utilizing U266B1 cell lines, mice peritoneal mast cell lines, ovalbumin-sensitized BALB/c mice and NC/Nga mice would be useful in evaluating candidate compositions for the purpose of treating allergic disease.

(2) In vivo Non-Allergic Inflammatory Response Model

Also at the time of filing, *in vivo* models useful for studying non-allergic inflammatory responses were well known to those of skill in the art. The specification provides an example of an established model for *in vivo* non-allergic inflammatory response analysis, which is described in further detail below. (*See* arachidonic acid-induced ear edema mouse model at Example 6 for *in vivo* non-allergic inflammatory response analysis in the specification.)

As discussed in Young, J.M. *et al.*, the arachidonic acid-induced ear edema mouse model is an established model for studying non-allergic inflammatory disease. *See* Young, J.M. *et al., J. Invest. Dermatol. 82*:367-371 (1984) (Exhibit G). Indeed, in recent years it has consistently been used as a non-allergic inflammatory *in vivo* model to illustrate the inhibitory effect of various plant extracts on inflammation-associated histamine release. *See* Kale, M. *et al., J. Ethnopharmacol. 112*:300-304 (2007) and Paula, A.C.B. *et al., Braz. J. Med. Biol. Res. 36*:105-112 (2003) (Exhibits H and I, respectively). As arachidonic acid is "capable of eliciting most aspects of the inflammatory response" with inflammatory reactions being "abrupt in onset and of short

duration," this *in vivo* model serves as a useful tool in showing how *Actinidia* extracts can inhibit non-allergic inflammatory responses, like edema, in such animals.

Therefore, Applicants submit that the state of the art was such that one of ordinary skill in the art at the time of filing would know that assays utilizing arachidonic acid-induced mice would be useful in evaluating candidate compositions for the purpose of treating non-allergic inflammatory disease.

c. The predictability or unpredictability of the art

Regarding the level of predictability of the art, the Examiner is of the opinion that "the art does not enable a person of ordinary skill in the art to make and use the claimed invention without resorting to undue experimentation." (Office Action at page 4). Here again, the Examiner does not support this blanket assertion with any objective technical evidence or reasoning.

In fact, the present specification adequately discloses methods by which a skilled person could determine whether an *Actinidia* kiwifruit extract administered-mammal exhibits inhibition or reduction in serum IgE levels and/or inhibition in serum histamine levels. As discussed above, Applicants have provided *in vitro* and *in vivo* models by which a person of ordinary skill in the art at the time of filing could i) measure serum IgE levels, ii) measure histamine production, iii) investigate the anti-allergic properties of a given composition, and iv) investigate whether a given composition is capable of inhibiting or reducing the symptoms of a non-allergic inflammatory disease. *See* specification at page 21, line 32 through page 30, line 20 of the specification. Therefore,

Applicants submit that all of the methods of the claimed invention can be practiced by a person of ordinary skill in the art without resorting to undue experimentation.

The Examiner also asserts that the term "inhibit" or "inhibiting" is synonymous with the term "curing" and that both of these terms circumscribe methods of treatment having absolute success. (Office Action at page 5). However, the Examiner fails to cite any basis for this construction of the term.

Applicants submit that the term "inhibit" must be construed in a manner that is consistent with the specification. In this case, that construction is consistent with the plain and ordinary meaning of the word. For example, *Webster's New International Dictionary* states that the term "inhibit" means "to hold back," "to check," "restrain" or "hinder." Accordingly, the plain and ordinary construction of the term "inhibit" in the context of the rejected claims means that IgE production and histamine release are inhibited/hindered to some degree, but does not require absolute cure or prevention.

This plain and ordinary construction is consistent with Applicants' usage of the term in the specification. For instance, the specification provides an *in vivo* Example where "inhibition" of edema, a symptom of non-allergic inflammatory disease, is observed in an arachidonic acid-induced ear edema mouse at an inhibition rate lower than 100%. *See* Example 6 of the specification. Indeed, Table 9 lists a 62.5% *inhibition rate* for edema in mice that were orally administered an *Actinidia* kiwifruit extract 1 hour prior to arachidonic acid application. Thus, it is clear from the specification that Applicants' use of the term "inhibit" in the claims is not intended to require absolute "cure" or "prevention" of the recited conditions.

d. The breadth of the claims

Regarding the breadth of the claims, the Examiner is of the opinion that "the Applicants fail to set forth the criteria that define the inhibition or reduction of IgE production and histamine release in a mammal." (Office Action at page 5). Applicants respectfully disagree with the Examiner.

The pending claims are directed to methods of inhibiting or reducing IgE production or inhibiting histamine release. Applicants respectfully submit that Experimental Example 2 is illustrative of an *in vivo* mouse allergy model that plainly shows reduction in serum IgE production when *Actinidia* extracts are orally administered. Experimental Example 4 is illustrative of reduction in serum IgE production in *human allergy patients* when *Actinidia* extracts are orally administered. Experimental Example 5 is illustrative of an *in vitro* allergy model that plainly shows inhibition of histamine production when *Actinidia* extracts are applied to IgE sensitized mast cells. Finally, Experimental Example 7 is illustrative of another *in vivo* mouse allergy model that plainly shows reduction in serum IgE production when *Actinidia* extracts are orally administered. Accordingly, Applicants submit that the specification provides sufficient guidance to not only enable a person of ordinary skill in the art to practice the full breadth of the claims, but also to test the efficacy of the claimed methods.

e. The amount of direction or guidance presented and the presence or absence of working examples

The Examiner asserts that the "[specification] does not provide any guidance in terms of inhibition or reduction of IgE production and histamine release in a mammal," and that the "applicant doses [sic] not provide any working examples for the inhibition or

reduction of IgE production and histamine release in a mammal." (Office Action at page 5). Not only is this assertion clearly incorrect, but no attempt has even been made by the Examiner to discuss any deficiency in the specification or to provide acceptable evidence or reasoning to back up these clearly erroneous assertions.

In contrast, Applicants submit that all of the working examples mentioned above, which include art-accepted models for assessing allergic and non-allergic inflammatory responses, plainly demonstrate the inhibitory activity of the extracts of the present invention. The Office Action points to no evidence indicating that those skilled in the art would question the predictability in the art based on the *in vitro* or *in vivo* activity of the working examples. *In re Wright,* 999 F.2d 1557, 1562, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993); *see also* M.P.E.P. § 2164.04.

It is respectfully submitted that the guidance provided in the specification is sufficient to enable one of ordinary skill to practice the invention without undue experimentation. Applicants respectfully submit that there is no issue of undue experimentation as it relates to working examples.

f. The quantity of experimentation necessary

Regarding the quantity of experimentation needed, the Examiner believes that the amount of experimentation necessary to reduce or inhibit IgE production or inhibit histamine release in a mammal in need thereof via the administration of an *Actinidia* kiwifruit extract "would be an undue burden to one of ordinary skill in the art and amount to the trial and error type of experimentation." (Office Action at page 6).

For the reasons mentioned above regarding factors a-e, Applicants respectfully submit that undue experimentation is not required to practice the invention. It would be

routine experimentation for one skilled in the art to practice the claimed invention based upon the teachings of the specification.

3. Summary

In order to establish a *prima facie* case of nonenablement, the Examiner bears the burden of presenting sufficient evidence and sound reasoning to show that the claimed invention is not enabled. *See Marzocchi*, 439 F.2d at 224, 169 USPQ at 370. The Office Action, however, is wholly lacking in any objective scientific evidence or technical reasoning that would refute or cast doubt on the enablement of the teachings in Applicants' specification. On the contrary, the claimed methods of inhibiting or reducing IgE production or inhibiting histamine release have been exemplified in Applicants' numerous Experimental Examples such that a person of ordinary skill in the art would have been able to practice the methods of the present claims without undue experimentation.

Accordingly, Applicants submit that the Examiner's reasons for the rejection are insufficient to establish a *prima facie* case of nonenablement and respectfully request that the rejection of claims 146, 149-176, 204, and 208-232 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

B. Rejections Under 35 U.S.C. § 103(a)

Claims 146-232 are rejected under 35 U.S.C. § 103(a), as allegedly being obvious over Murad (U.S. Pat. No. 6,630,163) in view of Endres *et al.* (DE 19758090 A1) and/or Udagawa (JP 61140510 A) and further in view of Wuthrich (*Clin. Exp. Allergy 8(3)*:241-

248), Lukacs *et al.* (U.S. Pat. Appl. No. 2002/0006410 A1), and Capetola *et al.* (U.S. Pat. No. 4,444,780). Applicants respectfully traverse the rejection.

1. Elements of a Prima Facie Case of Obviousness

In order to establish a *prima facie* case of obviousness, the Examiner must show that (1) all the claim limitations are either taught or suggested by the prior art; (2) there is some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill the art, to modify the reference or to combine reference teachings; and (3) a reasonable expectation of success while evaluating references based on the *Graham* factual inquiries. *See In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974); *In re Rouffet,* 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998); *In re Merch & Co., Inc.,* 800 F.2d 1091, 213 USPQ 375 (Fed. Cir. 1986); and *Graham v. John Deere Co.,* 38 U.S. 1, 148 USPQ 459 (1996). Additionally, when "formulating a rejection under 35 U.S.C. § 103(a) based upon a combination of prior art elements, it remains necessary to identify the reason that a person of ordinary skill in the art would have combined the prior art elements in the manner claimed." Memorandum from the United States Patent and Trademark Office, "Supreme Court decision on *KSR Int'l Co. v. Teleflex Inc.*," (May 3, 2007) at page 2.

Applicants respectfully submit that the Examiner has erred in determining the scope and content of the cited references and in ascertaining the differences between the claimed invention and the cited references. As such, Applicants believe the Examiner has failed to make out a *prima facie* case of obviousness.

2. Murad (U.S. Pat. No. 6,630,163)

As mentioned previously in Applicants' Amendment and Reply of April 10, 2008, Applicants submit that Murad merely mentions the use of fruit extracts generally to treat a multitude of non-allergic inflammatory skin diseases and mentions kiwi in a laundry list of fruits. Murad does not disclose treatment of ***allergic disease or non-allergic non-dermatological inflammatory diseases*** nor does it disclose the specific treatment of diseases recited in independent claims 146 and 176. As such, the reference does not teach all of the claim limitations of any of the pending claims.

3. Endres et al. (DE 19758090 A1)

While Endres mentions using *Actinidia arguta* extracts to treat non-allergic inflammatory dermatological conditions, Endres does not disclose treatment of ***allergic or non-allergic non-dermatological inflammatory disease*** with extracts of kiwifruit of the genus Actinidia, let alone the specific treatment of diseases recited in independent claims 146 and 176. Therefore, there is no suggestion or motivation to treat allergic or non-allergic non-dermatological inflammatory disease in a mammal in need thereof with kiwifruit extracts of the claimed invention simply by combining the Murad and Endres references.

a. Psoriasis and Allergic Skin Disease

At page 10 of the Office Action, the Examiner classifies psoriasis as an allergic disease to rebut Applicants' argument that Endres fails to teach allergic disease. However, the Examiner failed to provide any evidence to support this assertion and also erred in determining the content of the Endres reference. Applicants submit the

following discussion in an effort to explain the differences between psoriasis and allergic skin disease, using atopic dermatitis as an example.

Atopic dermatitis and psoriasis both affect the appearance of the skin and are sometimes misdiagnosed as the same disease. Both diseases have fundamental immune system defects and are often characterized, in part, by skin inflammation. The underlying molecular mechanisms of these two diseases, however, are completely different. In simple terms, psoriasis is a genetically predetermined, autoimmune condition mediated primarily by TNFα, presenting symptoms that include skin plaques that are not pruritic and not prone to infection. In contrast, atopic dermatitis is triggered by sensitization to environmental antigens, with inflammation mediated primarily by IL-4 and IL-13, presenting symptoms that include highly pruritic lesions that are prone to infection. *See* Christophers, E. and Henseler, T., *Arch. Dermatol. Res. 279 Suppl:*S48-S51 (1987) (Exhibit J). Additional details about these two conditions are given below.

Diseases involving inflammation are characterized by the influx of certain cell types and mediators, the presence of which can lead to tissue damage and sometimes death. Diseases involving inflammation are particularly harmful when they afflict certain organs and systems, such as the respiratory system, which can result in obstructed breathing, hypoxemia, hypercapnia and lung tissue damage, or in the skin, which can result in pruritis (itching), skin lesions, swelling, and scaling, or in joints, which can result in erosion and destruction of cartilage, collagen and bone. *See* Broide, D. and Sriramarao, P., *Immunol. Rev. 179*:163-172 (2002) (Exhibit K).

Allergic or atopic diseases as mentioned above are mediated in part by IgE, while T_H2 cells, mast cells and eosinophils are upregulated and play important roles in the

disease process. Allergic or atopic dermatitis is a chronic and relapsing inflammatory skin disease characterized by pruritic and eczematous skin lesions, along with elevated IgE levels associated with T_H2 upregulation. The skin lesions of atopic dermatitis patients demonstrate an infiltration of inflammatory cells including T lymphocytes, monocytes/macrophages, eosinophils and mast cells. *See* Leung, D.Y., *Clin. Exp. Immunol. 107 Suppl 1*:25-30 (1997) (Exhibit L).

Psoriasis is a chronic skin disorder characterized by periodic flare-ups of well-defined, red patches covered by a silvery, flaky scale on the arms, legs and the scalp. The most common type of psoriasis is chronic plaque psoriasis. The exact cause of psoriasis is unknown, but it is believed that a combination of several factors contributes to the development of this disease. *See* Nomura, I. *et al., J. Immunol. 171*:3262-3269 (2002) (Exhibit M).

Nine gene mutations are implicated in causing psoriasis. One of these mutations on chromosome 6, called PSORS-1, appears to be a major factor that can lead to psoriasis. With psoriasis, these gene mutations seem to largely affect T-helper cells. Normally, T-cells, when the T_H1 and T_H2 cytokines are in balance, produce chemicals that help heal the skin. In psoriasis, T-cells produce an abnormally large amount of these chemicals and actually cause more inflammation in the skin and joints. Upregulation of the T_H1 cytokines is implicated in this process. These T-cells "attack" the skin and set off a cascade of events that make the skin cells multiply so fast that they start to stack up on the surface of the skin. Normal skin cells form, mature, and then are sloughed off every 30 days. But in plaque psoriasis, the skin goes through this whole process in 3-6 days. Inflammatory processes induce the migration of IFNγ-producing T_H1 lymphocytes

into the skin. A primary involvement of T_H1 related cytokines is the most common observed cytokine imbalance in psoriasis. TNFα, a specific cytokine generally associated with T_H1 upregulation and inflammation is commonly associated with psoriasis. *See* Traub, M. and Marshall, K. *Alt. Med. Rev.* 12:319-330 (2007) (Exhibit N). As T_H1 cytokines play a greater role in the pathology of psoriasis, psoriasis cannot be classified as an allergic disease.

Accordingly, the Examiner has erred not only in asserting that psoriasis is an allergic disease but also in asserting that Endres teaches treating allergic diseases. Additionally, the references, even when combined, fail to provide a reasonable expectation of successfully treating *allergic or non-allergic non-dermatological inflammatory disease* by administering a kiwifruit extract to a mammal in need thereof.

4. Udagawa (JP 61140510 A)

Udagawa mentions the use of *Actinidia kolomikta* and *Actinidia polygama* fruit extracts in *cosmetics* but does not disclose the use of kiwifruit extracts or kiwifruit species' (*Actinidia arguta, Actinidia kolomikta* or *Actinidia polygama*) extracts for *oral administration*. Nor does Udagawa teach addressing the mechanism underlying allergic and non-allergic non-dermatological inflammatory disease or orally administering kiwifruit extracts to treat any condition to a mammal in need thereof, let alone the *allergic and non-allergic non-dermatological inflammatory conditions* of the present invention.

Again, there is no suggestion or motivation to treat *allergic or non-allergic non-dermatological inflammatory disease* with the claimed extracts of kiwifruit of the genus *Actinidia* simply by combining the Murad, Endres and Udagawa references.

Additionally, the references combined fail to provide a reasonable expectation for successfully treating allergic or non-allergic non-dermatological inflammatory disease by orally administering a kiwifruit extract to a mammal in need thereof.

5. Wuthrich (Clin. &. Exp. Allergy 8:241-248 ; Lukacs et al. (U.S. Pat. Appl. Publ. No. 2002/0006410); and Capetola et al. (U.S. Pat. No. 4,444,780 A)

The Examiner has additionally cited Wuthrich, Lukacs and Capetola. Applicants agree with the Examiner's assessment of Wuthrich and Capetola, but submit that these references do not cure the deficiencies of Murad, Endres and Udagawa.

The Examiner states that "Lukacs et al. is solely used to show that in treating inflammatory disease results in a decrease in the production of Th2-type antibody isotypes, such as IgG1 and IgE, and/or an increase in the production of Th1-type antibody isotypes, such as IgG2a or IgG3." (*See* Office Action at page 7). Applicants respectfully disagree with the Examiner's assessment of the content of the Lukacs publication.

The Examiner has erred in concluding that treating any inflammatory condition necessarily upregulates the production of T_H1-type antibody isotypes and downregulates the production of T_H2-type antibody isotypes. In fact, diseases that upregulate T_H2-type antibody isotypes are a subgenus of diseases in the genus of inflammatory conditions, and not every inflammatory condition can be treated simply by downregulating T_H2-type antibody isotypes and upregulating T_H1-type antibody isotypes. Applicants have shown in the above discussed case of psoriasis, an inflammatory disease, that inflammation cannot be treated simply by *further* upregulating T_H1-type antibody isotypes.

Furthermore, throughout the detailed description section of Lukacs are embodiments that are directed to administering agents that aim to treat inflammatory conditions associated with the upregulation of T_H2-type antibody isotypes rather than treating *any and all* inflammatory conditions and observing a shift from T_H2-type antibody isotype production to T_H1-type antibody isotype production. *See* paragraphs [0063]-[0065] of Lukacs. Also, Lukacs uses the same BALB/c ovalbumin-sensitized mouse model, an art-recognized *in vivo* allergy model, in Examples 1 and 2, to show the treatment of inflammation induced by the allergen, ovalbumin. Similarly, the remaining Examples (Examples 3-6) of Lukacs describe the use of *in vivo* mouse allergy models to treat inflammation induced by allergens. Lukacs discusses what is already known in the art by way of T_H1/T_H2 immune response mechanisms and further highlights the Applicants' use of BALB/c ovalbumin-sensitized mice models for studying allergic disease.

As such, Applicants submit that these references do not cure the deficiencies of Murad, Endres and Udagawa or aid in providing a reasonable expectation for successfully treating allergic or non-allergic non-dermatological inflammatory disease by orally administering a kiwifruit extract to a mammal in need thereof.

6. Product-By-Process Claim Format

The Examiner asserts that claims 159-167 and 188-196 are in a product-by-process format and as such are not limited to the extracts produced by a recited method. (Office Action at page 8). Applicants disagree with the Examiner's assertion.

The pending claims are directed to *methods of treating* allergic and specific non-allergic non-dermatological inflammatory diseases via the oral administration of kiwifruit

extracts to a mammal in need thereof. As discussed above, this particular use for kiwifruit extracts was not taught or suggested by the cited art. Therefore, the additional manufacturing process steps recited in claims 159-167 and 188-196 also do not render the claims obvious over the cited art.

7. ***Summary***

The Examiner asserts that the combination of Murad, Endres and Udagawa references renders obvious the pending claims. As explained above, the claimed methods are non-obvious because the cited references (1) do not teach the treatment of *allergic or non-allergic non-dermatological inflammatory* diseases via *oral* administration with kiwifruit *extracts*; (2) do not provide a suggestion or motivation for reference combination; (3) do not provide a reasonable expectation of success; and (4) are summarized inaccurately. As such, Applicants submit that the Examiner has failed to make a *prima facie* case of obviousness.

Accordingly, it is respectfully requested that the rejection of claims 146-232 under 35 U.S.C. § 103, as allegedly obvious, be reconsidered and withdrawn.

The Examiner has also rejected claims 146-148, 150-177, 179-206, and 208-232 under 35 U.S.C. § 103(a), as allegedly unpatentable over Forastiere *et al.* (*Thorax* *55*:283-288 (2000)) in view of Endres *et al.* (DE 19758090 A1) and/or Udagawa (JP 61140510 A). Applicants respectfully traverse the rejection.

1. Forastiere et al. (Thorax 55:283-288 (2000))

As stated in Applicants' Supplemental Amendment of June 3, 2008, Applicants reiterate that Forastiere merely discusses treating asthma symptoms by administering common kiwifruit. This reference does not disclose administering any specific type of kiwifruit *extract*, let alone the kiwifruit extracts from *Actinidia arguta, Actinidia polygama* and *Actinidia kolomikta*. Nor does this reference teach alleviating the symptoms of *anaphylaxis, allergic rhinitis, allergic conjunctivitis, allergic dermatitis, atopic dermatitis, contagious dermatitis, urticaria, insect allergy, food allergy or drug allergy* by administering kiwifruit extracts. Thus, Forastiere fails to teach each and every limitation of the pending claims.

Additionally, Applicants submit that the Examiner has erred in assessing the content of the Forastiere reference. Forastiere mentions that while a "clear association between a low intake of oranges and other vitamin C containing fruits during winter and an increased risk of wheezing symptoms in children" is evident, "the protective effect [of kiwifruit consumption] does not appear to be dose related." *See* Forastiere *et al.* at page 286. Rather than attributing the wheezing attenuation to any special unidentified chemical in the administered kiwifruit, Forastiere suggests that these "findings confirm previous evidence in adults that low dietary vitamin C is associated with increased symptoms of bronchitis and wheezing." *See* Forastiere *et al.* at page 287. In fact, the remainder of the discussion section in the Forastiere reference is devoted to vitamin C intake. Accordingly, one of ordinary skill in the art after reading the Forastiere reference would attribute observed wheezing attenuation to vitamin C consumption and that the

relationship between vitamin C consumption and asthmatic symptoms was not one that was dose-related.

In contrast to the teachings of Forastiere, Applicants submit that the kiwifruit extracts used in the claimed methods do induce dose-related responses. Applicants' post-filing data shows that when kiwifruit extracts (at 0, 0.5, 1, and 2 mg/mL doses) prepared according to the methods outlined in the specification were applied to human U266B1 myeloma cells (an art-established *in vitro* model for studying allergic responses) that had been previously stimulated with lipopolysaccharide, a dose-dependent reduction of IgE production was observed (as measured by ELISA). *See* Kim, D. *et al., Clin. Exp. Allerg. 39*:280-289 (2009) (Exhibit O). Similarly, when kiwifruit extracts (at 0, 0.5, 1, and 2 mg/mL doses) prepared according to the methods outlined in the specification were applied to rat mast cell line RBL-2H3 that has been previously stimulated with a calcium ionophore, A23187, a dose-dependent reduction of IL-4 production was observed (as measured by ELISA). *See* Kim, D. *et al., Int. Arch. Allerg. Immunol.* (submitted) (Exhibit P).

As discussed above, Applicants submit that neither Endres nor Udagawa teach each and every claim limitation of the pending claims. Additionally, neither reference teaches the mechanism underlying allergic disease or orally administering kiwifruit extract to treat any allergic or non-allergic non-dermatological inflammatory disease in a mammal in need thereof, let alone the ***allergic or non-allergic non-dermatological inflammatory conditions*** of the present invention.

For the reasons provided above, Applicants assert that there is no suggestion or motivation to combine Forastiere, which teaches attenuation of asthmatic symptoms via

a threshold level of vitamin C consumption with either Endres or Udagawa. Moreover, a skilled person in the art would not have had a reasonable expectation of achieving the desired therapeutic results based solely on the cited references.

2. Lee et al. (Clin. Immunol. 101:220-228 (2001))

The Examiner asserts that "Lee et al. is solely used to show that allergic asthma is associated with histamine release, serum IgE, IgG1, IgG2, Th2, and Th1 levels," and "to show the relationship between asthma and edema." (*See* Office Action at page 9.)

Again, Applicants agree with the Examiner's assessment and submit that this statement is also consistent with Applicants earlier discussion relating to the molecular basis of allergic disease. However, Applicants respectfully submit that the Lee *et al.* reference does not cure the deficiencies of the Forastiere, Endres or Udagawa references.

3. Consumption of Kiwifruit and "crude extract" Claim Limitation

The Examiner asserts that "[c]onsuming kiwi fruit as a food meets the limitation 'crude extract' of the instant claims." (*See* Office Action at pages 8-9). Applicants respectfully disagree with the Examiner's assertion.

Here again, Applicants submit that the term "crude extract" must be construed in a manner that is consistent with the specification. While the Examiner believes that consuming kiwifruit meets the claim limitation of "crude extract," the specification states at page 6, line 34 through page 7, line 1, that the "crude extract of hardy kiwifruit can be obtained by using water, lower alcohols such as methanol, ethanol and the like, or the mixtures thereof, preferably distilled water or 70% ethanol soluble extract and above non-polar solvent soluble extract therefrom can be obtained by using non polar solvent such as hexane, ethyl acetate or dichloromethane solvent." The specification also

provides more detailed methods by which crude extracts may be obtained at page 7, lines 20-32.

Additionally, the composition that results from mastication is not the same as the one disclosed by the present application. The kiwifruit "crude extract" described by the Examiner consists of kiwifruit juice, water, salts, and enzymes among other non-preferred chemicals.

Accordingly, Applicants submit that 1) the Examiner's construction of "crude extract" is incorrect, 2) the Examiner's kiwifruit extract example differs substantially from the extract disclosed by the present application, and 3) the normal meaning of extract does not encompass simply eating fruit.

4. Product-By-Process Claim Format

The Examiner repeats the assertion that claims 159-167 and 188-196 are in a product-by-process format and "as such as not limited to the extracts produced by a recited method." Here again, Applicants disagree with the Examiner's assertion.

The pending claims are directed to ***methods of treating*** allergic and specific non-allergic non-dermatological inflammatory diseases via the oral administration of kiwifruit extracts to a mammal in need thereof. As discussed above, this particular use for kiwifruit extracts was not previously known or disclosed by Forastiere, Endres or Udagawa. Therefore, the additional manufacturing process steps recited in claims 159-167 and 188-196 also do not render the claims obvious over the cited art.

5. Summary

The Examiner asserts that the combination of Forastiere, Endres and Udagawa references renders obvious the pending claims. As explained above, the claimed

methods are non-obvious because the cited references (1) do not teach methods of treating ***allergic or non-allergic non-dermatological diseases*** via the ***oral*** administration of kiwifruit ***extracts***; (2) do not provide a suggestion or motivation for reference combination; (3) do not provide a reasonable expectation of success; and (4) are summarized inaccurately. As such, Applicants submit that the Examiner has failed to satisfy the factual inquiry requirements as set forth in *Graham* and consequently has failed to make a *prima facie* case of obviousness.

In view of the claim amendments and the comments provided above, it is respectfully requested that the rejection of claims 146-148, 150-177, 179-206, and 208-232 under 35 U.S.C. § 103, as allegedly obvious, be reconsidered and withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Timothy J. Shea, Jr.
Attorney for Applicants
Registration No. 41,306

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1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600
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